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Tallysomycin $S_{10}b$ – a phase I trial

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Summary. Tallysomycin $S_{10}b$ is a new bleomycin analogue. In animal studies it has shown the same degree of antineoplastic activity as bleomycin; however in contrast to that of bleomycin, its dose-limiting effect in animal systems is renal toxicity and its pulmonary toxicity is less pronounced. A total of 16 patients received tallysomycin $S_{10}b$ at three exploratory levels: 3 patients were given a dose of 1.25 mg/m^2, 9 received 2.5 mg/m^2 and 4 were given 5 mg/m^2 as i.v. bolus injections twice weekly. Before treatment and every 3 weeks, plain chest X-rays, pulmonary function tests, renography and ^{51}Cr-EDTA clearance were carried out. No renal toxicity was found in any of the treatment groups. In the first two groups no changes in chest X-rays were observed during treatment, whereas in the third group a decrease in single-breath carbon monoxide diffusion capacity (DL_{CO}) was seen in one patient until the treatment was discontinued. Two of four patients receiving 5 mg/m^2 developed interstitial pneumonitis at total doses of 104 and 160 mg, respectively. During the trial no haematologic or hepatic changes occurred due to the drug. The frequency of occurrence of skin changes, stomatitis and fever increased with the cumulative dose of tallysomycin $S_{10}b$, and these side effects were similar to those seen with bleomycin. No tumor regression was seen during the trial. In contrast to the findings in previous animal studies, we found that the dose-limiting effect was pulmonary and not renal toxicity. The recommended dose for further phase II trials is 2.5 mg/m^2 twice weekly, with careful monitoring of the pulmonary function.

Introduction

As bleomycin has shown significant activity against malignant diseases such as testicular cancer [9] and malignant lymphoma [1, 10], a search for new bleomycin analogues with reduced pulmonary toxicity and/or higher or broader antitumor activity has been initiated. Tallysomycin $S_{10}b$ is an antibiotic structurally related to bleomycin, from which it differs by the presence of an amino sugar (4-amino-4,6-dideoxy-L-talose), a longer peptide chain and a shorter terminal amino group (Fig. 1).

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The antitumor activity of tallysomycin $S_{10}b$ has been found to be equivalent to or stronger than that of bleomycin in various experimental animal systems [12, 13]. Its antitumor effect and acute toxicity have been tested in P-388 lymphatic leukemia in mice [12]. When compared with bleomycin, tallysomycin $S_{10}b$ was about 4 times more toxic but 11 times more active than the parent drug, suggesting a threefold gain in therapeutic index. In contrast to that of bleomycin, the dose-limiting factor of tallysomycin $S_{10}b$ in previous animal studies was progressive and irreversible nephrotoxicity, and its pulmonary toxicity appeared to be less pronounced than that of bleomycin [2, 3, 7, 11]. Neither bone marrow suppression nor cardiomyopathy has been observed [16]. Pharmacokinetic studies [4, 6] have shown that, in contrast to bleomycin, only 10% of the tallysomycin $S_{10}b$ dose is excreted by the kidneys and that this bleomycin analogue has a gamma phase that is not seen in the parent drug. Based on this information, tallysomycin $S_{10}b$ was selected from a series of analogues for a phase I trial.

Material and methods

Regimen. Tallysomycin $S_{10}b$ was supplied as a hydrochloride salt in vials containing 10 mg tallysomycin $S_{10}b$ base and 100 mg mannitol (courtesy of Bristol-Meyers Ltd, Copenhagen). Based on the results of the preclinical safety evaluation studies [3], nephrotoxicity is considered to be its dose-limiting toxicity.

Under the guidelines of the Federal Drug Administration the proposed initial dose in humans would be either 10% of the LD_{10} in the mouse or 1/3 of the lowest toxic dose (TDL) in the dog. The single-dose 10% LD_{10} in the mouse was determined to be 13.5 mg/m^2, but this dose was toxic in the dog. One-third of the single-dose TDL in the dog was estimated to be 2.2 mg/m^2. Consequently, the initial i.v. dose of tallysomycin $S_{10}b$ was stipulated to be 1.25 mg/m^2 given twice weekly as a bolus injection. The present study was planned with dose escalation, exploring dose levels of 1.25, 2.5 and 5 mg/m^2 and including at least three patients at each dose level. When unacceptable toxicity occurred at any dose, that level was abandoned and the study was resumed at the next lower dose

Stomatitis, skin ulceration and sclerosis were expected: if they were observed, treatment with tallysomycin $S_{10}b$ was discontinued until all signs of toxicity had resolved, whereupon treatment was resumed at the same dose level.

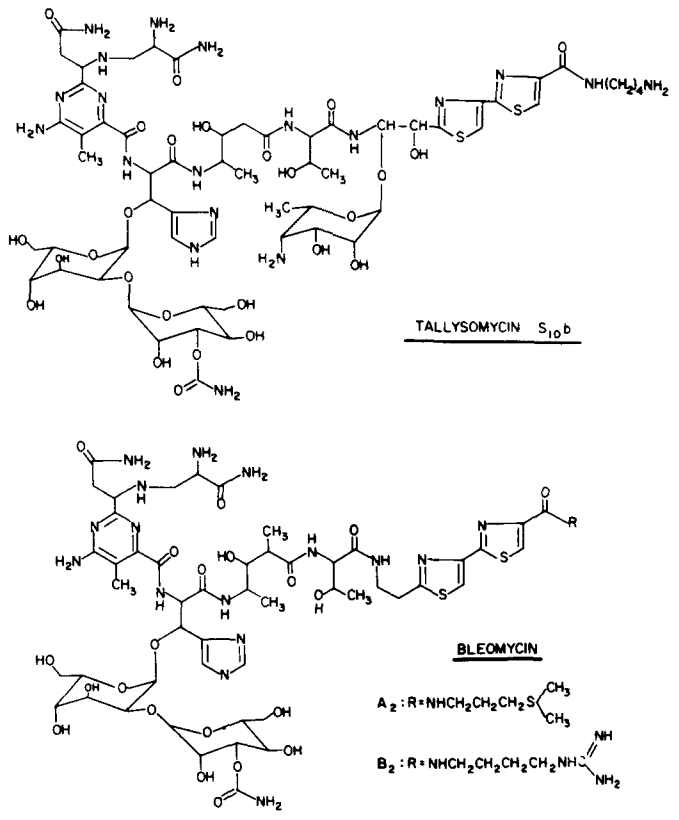

Fig. 1. Chemical structures of tallysomycin $S_{10}b$ and bleomycin

Short-term fever was treated with salicylates and did not lead to discontinuation of tallysomycin $S_{10}b$. Treatment was stopped if the patient developed clinical evidence of pulmonary toxicity or if significant radiographic changes became apparent in serial chest X-rays.

Patients. Minimal haematologic requirements for inclusion in the study consisted of a platelet count of $>100{,}000/mm^3$ and a white blood cell count of $>3{,}500/mm^3$. In addition, the results of hepatic biochemical tests such as serum glutamic oxaloacetic transaminase (S-GOT), S-basic phosphatase, and prothrombin had to be normal. Serum creatinine, ^{51}Cr-EDTA clearance and renal distribution as assessed by renography were also required to be within normal ranges. Patients previously treated with bleomycin, cisplatin or chest irradiation were excluded from the study. All patients had progressive solid tumors for whom no effective treatment was known. Informed consent was obtained from all patients before treatment, which in all cases was given on an outpatient basis.

A clinical examination was done before the start of therapy and every 2 weeks thereafter. Complete blood cell counts, serum electrolytes, serum creatinine, S-GOT, serum alkaline phosphatase, serum lactate dehydrogenase, serum bilirubin and prothrombin time were analyzed every other week. Plain chest roentgenograms and spirometry, including a single-breath helium dilution manoeuvre, were carried out using a Jaeger computing pulmonary system before therapy and every 3 weeks thereafter. Total lung capacity, vital capacity residual volume, forced vital capacity and forced expiratory volume in 0–1 s were measured. Single-breath carbon monoxide diffusion capacity (DL_{CO}) was determined by a modified method of Ogilvie et al. [8]. All DL_{CO} values were corrected according to haemoglobin (Hb) concentrations by the method of Dinakara et al. [5]. Before treatment and every 3 weeks thereafter, renography was done ^{51}Cr-EDTA clearance was determined.

Objective remission and progression of the disease during therapy were evaluated according to WHO recommendations [17]. For statistical analyses Student's *t*-test for paired samples and linear regression analyses were used.

Results

A total of 16 patients with a median age of 59 years (range, 37–69 years) were included in the study (Table 1). In all, 11 of the patients had malignant abdominal tumors, 4 had primary lung tumors and 1 had a disseminated malignant melanoma. All patients had measurable tumors, but tumor regression was not observed in any of the patients.

Table 1. Patient characteristics

Patient number	Age	performance status	Site of primary tumor	Lung involvement	Previous chemotherapy	Dose/ total	Hb (mmol/l)		DL_{CO} (ml/min mmHg)		GFR (ml/min)	
							before	after	before	after	before	after
1	47	2	rectum	+	+	1.25/140	7.7	5.1	23.6	19.1	97	91
2	42	2	rectum	−	+	1.25/34	8.0	7.1	17.9	15.8	122	119
3	45	2	rectum	−	−	1.25/48	8.3	6.9	26.6	24.4	141	105
4	46	2	lung	+	−	2.5 /112	6.8	6.4	8.6	11.4	89	89
5	55	2	rectum	−	−	2.5 /36	8.2	7.8	14.7	14.4	84	72
6	67	2	rectum	+	−	2.5 /120	8.6	8.1	22.6	22.5	95	81
7	37	2	rectum	+	+	2.5 /68	6.7	6.4	26.1	25.2	86	85
8	65	2	mesothelioma	+	+	2.5 /81	6.8	6.4	16.6	21.1	87	100
9	64	2	rectum	−	+	2.5 /40	8.7	7.8	20.9	17.3	83	78
10	65	2	carcinoid	−	+	2.5 /73	7.9	8.8	26.7	27.4	73	63
11	49	2	rectum	−	+	2.5 /103	7.7	8.6	35.5	31.1	85	88
12	53	2	lung	+	+	2.5 /90	9.3	8.5	28.3	21.2	106	110
13	61	2	lung	+	−	5 /175	7.3	7.2	20.6	16.2	70	78
14	69	2	melanoma	−	−	5 /120	8.5	7.2	21.8	10.7	69	78
15	59	2	rectum	−	−	5 /180	8.5	7.7	26.0	27.2	121	117
16	62	2	pancreas	−	+	5 /104	7.3	6.2	19.2	9.1	81	71

Pulmonary toxicity

The first three patients received 1.25 mg/m^2 tallysomycin S_{10}b twice weekly, for a total dose ranging from 27–112 mg/m^2. No significant changes were observed in serial lung or kidney function studies or serial chest X-rays during treatment. None of these patients developed dyspnoea, tachypnoea, nonproductive cough or fine rales on auscultation of the lungs. All patients died of their malignant disease in other institutions; no postmortem histologic examinations were carried out.

At the second dose level nine patients received 2.5 mg/m^2 tallysomycin S_{10}b twice weekly, for a cumulative total dose ranging from 15–48 mg/m^2. In patient 12 the DL_{CO} constantly decreased with the accumulated dose of tallysomycin S_{10}b, without a detectable change in serial chest X-rays or the dynamic or static volumes of the lungs. When the decrease in DL_{CO} exceeded 35%, treatment was stopped and no further decrease or increase in DL_{CO} was seen.

At the third dose level four patients received 5 mg/m^2 tallysomycin S_{10}b twice weekly, for a total dose ranging from 18 to 32 mg/m^2. In patients 14 and 16 a constant decrease in DL_{CO} was seen with increasing dose. These patients developed clinical symptoms of dry cough dyspnoe and treatment was discontinued; both subsequently developed patchy lung infiltration. In addition, both patients manifested tachycardia and oedema of the lower extremities but no significant changes in blood pressure. No electrocardiographic changes were observed during treatment. In both cases treatment with digoxin was initiated and the peripheral oedema disappeared; however, the decrease in DL_{CO} was sustained together with the X-ray changes. These patients died shortly thereafter without any improvement in chest X-rays. No autopsies were carried out.

Renal toxicity

During treatment, no decrease in glomerular filtration rate as measured by ^{51}Cr-EDTA clearance or renal blood flow as measured by renography that could be ascribed to treatment with tallysomycin S_{10}b was detected in any of the three groups.

Other toxicities.

As summarised in Table 2, hyperpigmentation, skin ulceration and stomatitis were observed at all three dose levels; these toxicities increased with increasing dose of tallysomycin S_{10}b. The changes vanished within 14 days after the discontinuation of treatment. Neither haematologic suppression nor changes in hepatic biochemical tests were observed. Total alopecia was not observed, but minor hair loss was seen at all dose levels, as were anorexia and nausea. Fever was common after the first infusion of drug, with a maximum of 39° C, but it subsided in about 6 h and was abolished in the next treatment course by the administration of aspirin.

Table 2. Toxicities of tallysomycin S_{10}b in 16 patients

	1.25 mg/m^2	2.5 mg/m^2	5 mg/m^2
Hyperpigmentation of the skin	0/3	6/9	3/4
Ulceration	0/3	2/9	2/4
Stomatitis	0/3	2/9	2/4
Nausea and vomiting	2/3	3/9	4/4
Anorexia	2/3	5/9	4/4
Fever	0/3	1/9	0/4
Haematologic suppression	0/3	0/9	0/4
Hepatologic changes	0/3	0/9	0/4
Renal changes	0/3	0/9	0/4
Pulmonary X-ray changes	0/3	2/9	2/4
Pulmonary function changes	0/3	1/9	2/4
Cardiac incompensation	0/3	1/9	2/4

Discussion

Bleomycin has an established position in the treatment of various malignant diseases, and its various side effects are well described. As this drug is often a constant part of the treatment of lymphoma and testicular cancer, it is important to minimise its pulmonary toxicity without compromising its antineoplastic effects.

Two major approaches have tried to overcome this serious problem. The first is to monitor carefully the pulmonary function of the patient undergoing bleomycin treatment. It has been established that the maximal recommended dose of bleomycin is 170 mg/m^2 when the drug is given twice weekly and that the carbon monoxide diffusion capacity is presently the best parameter for describing subclinical pulmonary changes during bleomycin treatment [14, 15].

The other approach is to change the chemical structure of bleomycin to reduce its side effects without diminishing its antineoplastic effects. A series of bleomycin analogues have been developed, of which tallysomycin S_{10}b has shown the same antineoplastic activity in animal studies as bleomycin; however, in contrast to that of bleomycin, the dose-limiting effect of tallysomycin S_{10}b is renal toxicity and its the pulmonary toxicity is less pronounced.

The results of the present phase I trial, in contrast to those of previous animal studies, inidcate that the dose-limiting effect of tallysomycin S_{10}b in humans is pulmonary and not renal toxicity. At the first two dose levels of 1.25 and 2.5 mg/m^2, neither pulmonary nor renal toxicity was observed. At the third dose level (5 mg/m^2), patients 14 and 16 underwent a decrease in DL_{CO} with increasing dose and developed chest X-ray changes compatible with interstitial pneumonitis. Furthermore, both patients developed distal oedema but no electrocardiographic changes during treatment. They were treated with digitalis and diuretics and the oedema vanished; however, the decrease in DL_{CO} continued and both patients died shortly thereafter.

After two cases of severe – most likely lethal – pulmonary toxicity at 5 mg/m^2 twice a week, this dose level was abandoned and the study was resumed at a dose of 2.5 mg/m^2 twice a week. At this dose, patient 12 developed an irreversible decrease in DL_{CO} of more than 35% during treatment, but there were neither symptomatic nor radiologic signs of pulmonary toxicity. As the patient also developed right cardiac incompetence treatment was discontinued.

In a comparable study by Comis et al. [4] using tallysomycin S_{10}b two patients presented with mild, reversible pulmonary toxicity: one developed dyspnoe with bilateral pulmonary rales and interstitial fibrosis as determined by chest X-ray, and the other had shortness of breath and rales on physical examination but no changes in chest X-ray or DL_{CO}.

In conclusion, we found that tallysomycin $S_{10}b$ given at the three dose levels studied showed no renal toxicity, whereas pulmonary toxicity was severe at the highest dose; with respect to other side effects, the drug was equivalent to bleomycin. The recommended dose for further phase II trials is 2.5 mg/m^2 given i.v. twice a week, with careful monitoring of pulmonary function.

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